Peer Review File

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Response to comments of Reviewer A

First of all, we sincerely thank you for your appreciation of this manuscript and your recognition of the methodology. For your comments, our responses are as follows:

Comment 1: Some additional English language editing would give the paper the ultimative polish.

Reply 1: As suggested, we revised the whole manuscript carefully to avoid language errors, and we have polished the language of the manuscript.

Changes in the text: We marked the modified places with red font (please see full text).

Response to comments of Reviewer B

Thank you for your comments and suggestions concerning our manuscript. The comments and suggestions are all valuable and very helpful for revising and improving our manuscript. We have taken all these comments and suggestions into account as follows:

Comment 1: Intro: The authors may mention that intact FGF23 levels in early kidney disease are also driven by inflammation (e. g. Egli-Spichtig, Kidney Int 2019)

Reply 1: We have read this paper (Egli-Spichtig, Kidney Int 2019) carefully. The tumor necrosis factor-alpha mentioned in it can stimulate the production of plasma FGF23 levels in mouse model of CKD, which provide the explanation of FGF23 regulation. As suggested, we have added this point to our revised manuscript.

Changes in the text: we have modified our text as advised (please see Page 4, line 75).

Comment 2: Intro, l78-9; whether FGf23 is a determinant or only associated with cardiovascular disease is still a matter of debate, I suggest to rephrase more cautiously.

Reply 2: Thank you for your comment. We did not accurately describe the relationship between FGF23 and cardiovascular disease. After re-reading literatures, we changed our argument to "high serum intact FGF23 concentration is associated with the increased cardiovascular morbidity and mortality in patients with CKD".

Changes in the text: we have modified our text as advised (please see Page 5, lines 82-84).

Comment 3: Intro, l 84, targeting FGf23 does not likely postpone CKD but may help to improve its consequences

Reply 3: Thank you for your advice. According to your suggestion, we have changed our argument to "Reduction of high intact FGF23 concentration is a strategy, possibly improving the consequences of CKD".

Changes in the text: we have modified our text as advised (please see Page 5, line 85)

Comment 4: Results, l175-242, these data are summarized in table 1 and could be briefly summarized without details

Reply 4: We have deleted these duplicate information, and guided readers to look for more information in Table 1.

Changes in the text: we have modified our text as advised (please see Page 10, line 180).

Comment 5: A major limitation of this meta-analysis is the overall low number of observations in the different subgroups.

Reply 5: Thank you very much for pointing out the limitation of this paper. Because of the research we were able to retrieve the strict inclusion and exclusion criteria, we

included low number of observations in the different subgroups. We can't solve this problem right now, but we will update this meta-analysis when more clinical studies about phosphate binders are published in the future.

Changes in the text: We have mentioned these reasons in the discussion, so there is no change in our paper.

Comment 6: the duration of P-binder studies should be taken into account. Did the authors control for the duration of trials?

Reply 6: In this study, we did not control the duration of phosphate binders. Under the strict inclusion and exclusion criteria, the meta-analysis itself included fewer studies. If the duration is controlled, the sample size may be further reduced, and the credibility of the meta-analysis results may be greatly decreased. We carefully reviewed each original study, but many studies only report baseline and outcome data. Therefore, it is difficult to obtain intermediate data.

Changes in the text: We added a description of the duration of phosphate binders (please see Page 13, lines 239-244).

Comment 7: What about P-binder dosing?

Reply 7: Our study did not control the exact dosage of phosphate binders, but the dosage was within a similar range in included studies. For reasons, when phosphate binders are used to improve the consequences of CKD, their dosages depend on serum phosphorus concentration in patients. In the original study, the dosage of phosphate binders was different according to the state of the patients. The dosage is decreased when phosphate binders cause side effect, and is increased during high serum phosphorus concentration in each study. Generally, the dosage of phosphate binders is relatively consistent for

CKD patients with similar serum phosphorus concentration, for example, the dosage of lanthanum carbonate is usually 3 g/d for patients with CKD stages 3 to 5 (49,50). Since only patients with CKD stages 3 to 5 were included in our study, the dosage change of phosphate binders between different studies was small, which further weakened the effect of the dosage on the meta-analysis results. Thus, the credibility of our meta-analysis was relatively high.

49. Isakova T, Gutiérrez OM, Smith K, et al. Pilot study of dietary phosphorus restriction and phosphorus binders to target fibroblast growth factor 23 in patients with chronic kidney disease. Nephrol Dial Transplant, 2011. 26(2): p. 584-91.
50. Sprague SM, Abboud H, Qiu P, et al. Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial. Clin J Am Soc Nephrol, 2009. 4(1): p. 178-85.

Changes in the text: We added a description of the dosage of phosphate binders (please see Page 13, lines 244-257 and Table 3).